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NEW THYRONAMINE DERIVATIVE AND ITS SALTS, THEIR METHOD OF PREPARATION AND THEIR APPLICATION AS MEDICATIONS

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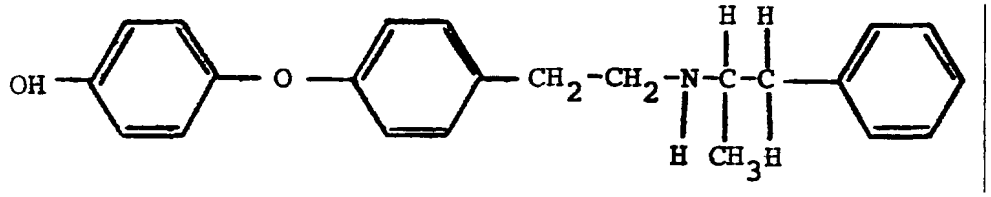
The present invention, in the making of which Pierre Henri Derible, André Poittevin and Robert Fournex participated, relates to a new thyronamine derivative, its salts, the method of preparation and the application of said products as medications.

The object of the invention is 4-(p-hydroxyphenoxy)-N-(α-methylphenethyl)phenethylamine having the formula:



as well as its acid addition salts.

Among the acid addition salts that may be preferably cited are those obtained from inorganic acids such as hydrochloric acid, hydrobromic acid, hydriodic acid, sulfuric acid, phosphoric acid, carboxylic acids such as acetic acid, maleic acid, fumaric acid, lactic acid,

succinic acid, tartaric acid, citric acid, benzoic acid or sulfonic acids such as methanesulfonic or p-toluenesulfonic acids.

Considered more specifically among the products and objects of the invention are the following:

- 4-(p-hydroxyphenoxy)-N-(α-methylphenethyl)phenethylamine;
- 4-(p-hydroxyphenoxy)-N-(α-methylphenethyl)phenethylamine hydrochloride;
- 4-(p-hydroxyphenoxy)-N-(α-methylphenethyl)phenethylamine lactate.

According to the invention, 4-(p-hydroxyphenoxy)-N-(α-methylphenethyl)phenethylamine and its salts can be obtained by a method characterized in that p-hydroxyphenoxyphenethylamine is reacted with benzyl methyl ketone, in the presence of a reducing agent, in order to obtain 4-(p-hydroxyphenoxy)-N-(α-methylphenethyl)phenethylamine which, if desired, is treated with an inorganic or organic acid to form the salt thereof.

In a preferred embodiment of the method of the invention, the p-hydroxyphenoxyphenethylamine is produced *in situ* via the action of an inorganic or organic base on a salt of p-hydroxyphenoxyphenethylamine.

For example, the base may be sodium hydroxide, potassium hydroxide, lithium hydroxide, ammonium hydroxide or triethylamine.

The reducing agent, for example, may be hydrogen, and the reaction preferably takes place in the presence of a catalyst such as platinum dioxide, for example.

The reaction is preferably carried out in an organic solvent, such as methanol, ethanol, propanol, benzene or toluene, for example.

It is likewise possible to prepare any salt of 4-(p-hydroxyphenoxy)-N-(α-methylphenethyl)phenethylamine from another salt of this same base, e.g., from hydrochloride which is reacted with a base, e.g., such as sodium hydroxide or ammonium hydroxide, and then the acid of the desired salt.

The products, and object of the present invention, have valuable pharmacological properties. They exhibit a clear vasodilating activity, which, in particular, results in the stimulation of tissue perfusion.

These properties justify their therapeutic application and, as a medication, another object of the invention is 4-(p-hydroxyphenoxy)-N-(α-methylphenethyl)phenethylamine, as well as its addition salts with pharmaceutically acceptable acids, e.g., such as 4-(p-hydroxyphenoxy)-N-(α-methylphenethyl)phenethylamine hydrochloride and 4-(p-hydroxyphenoxy)-N-(α-methylphenethyl)phenethylamine lactate.

These properties render them suitable for use in human or animal medicine, specifically for treating arteritis of the limbs, circulatory disturbances of the extremities, strokes and cerebrovascular insufficiency.

The usual adult dosage, which may vary depending on the product used, the subject treated and the illness involved, may, for example, consist of 1-500 mg per day, administered intravenously.

Another object of the present application are pharmaceutical compositions which, as an active principal, contain at least one of the aforementioned medications. These compositions are made such that they are capable of being administered via the digestive or parenteral route. They may be liquid or solid and appear in pharmaceutical forms routinely used in human medicine, e.g., such as plain or sugar-coated tablets, capsules, granules, suppositories or injectable preparations; they are prepared according to the usual methods.

The active principle or principles may be incorporated into excipients commonly used in these pharmaceutical compositions, such as talc, gum Arabic, lactose, starch, magnesium stearate, cocoa butter, aqueous or nonaqueous vehicles, fats of animal or vegetable origin, paraffin derivatives, glycols, the various wetting, dispersing or emulsifying agents and preservatives.

The examples below illustrate the invention, however without limiting it.

Example 1: 4-(p-hydroxyphenoxy)-N-(α-methylphenethyl)phenethylamine hydrochloride

10 g of p-hydroxyphenoxyphenethylamine hydrochloride are dissolved with heat in a mixture of 300 mL of ethanol and 10 mL of triethylamine, and then cooled to 20°C; 10 mL of benzyl methyl ketone are added, then 1 g of platinum dioxide. Hydrogenation is carried out until absorption is complete, the platinum is suction-filtered, allowed to dry, and the residue is taken up in 100 mL of ethyl acetate, then washed with water, dried completely and then taken up with 20 mL of ethyl acetate; 50 mL of a saturated solution of hydrochloric acid in ethyl acetate is added, suction-filtered, washed with ethyl acetate and then ether, then dried, yielding 13 g of product that are purified by recrystallization in isopropanol, yielding 7.6 g of 4-(p-hydroxyphenoxy)-N-(α-methylphenethyl)phenethylamine hydrochloride. MP = 170-171°C.

Analysis:	$C_{23}H_{26}ClNO_2$			
Calculated:	C % 71.96	H % 6.82	Cl % 9.23%	N 3.65%
Found:	72.1	6.9	9.2	3.5

Example 2: (p-hydroxyphenoxy)-N-(α-methylphenethyl)phenethylamine

900 cc of ethanol, 30 g of p-hydroxyphenoxyphenethylamine and 30 cc of triethylamine are mixed together, to which 30 mL of benzyl methyl ketone and 3 g of platinum dioxide at 20°C are then added. Hydrogenation is carried out until absorption is complete, the catalyst is filtered, the filtrate is dried and 58.1 g of raw product are obtained, which is dissolved in the ethyl acetate; a saturated solution of hydrochloric acid in ethyl acetate is added, the hydrochloride obtained is suction-filtered, recrystallized in isopropanol, treated with sodium hydroxide and

32.5 g of 4-(p-hydroxyphenoxy)-N-(α-methylphenethyl)phenethylamine are obtained. MP = 104°C.

Example 3 : 4-(p-hydroxyphenoxy)-N-(α-methylphenethyl)phenethylamine lactate

1 g of 4-(p-hydroxyphenoxy)-N-(α-methylphenethyl)phenethylamine is dissolved in 5 mL of ethyl acetate, a 10% solution of lactic acid in ethyl acetate is added until a pH of 3.5 is reached, the solution is cooled, suction-filtered, washed with ethyl acetate and dried; 0.9 g of product is obtained, which is recrystallized in 80 mL of ethyl acetate, yielding 0.760 g of 4-(p-hydroxyphenoxy)-N-(α-methylphenethyl)phenethylamine lactate. MP = 136°C.

Analysis:	$C_{26}H_{31}NO_5$		
Calculated:	% C 71.38	% H 7.14	% N 3.20
Found:	71.3	7.3	3.1

Using the same method, but by crystallizing in isopropanol, highly pure 4-(p-hydroxyphenoxy)-N-(α-methylphenethyl)phenethylamine lactate is obtained. MP = 160°C.

Analysis:			
Calculated:	% C 71.38	% H 7.14	% N 3.20
Found:	71.3	7.2	3.0

Example 4: Preparation of a pharmaceutical composition

An injectable solution was prepared having the following formula:

- 4-(p-hydroxyphenoxy)-N-(α-methylphenethyl)phenethylamine hydrochloride.....10 mg;
- Aqueous excipient qs.....1 cc.

Pharmacological study

The pharmacological study involved the following 2 products:

- Product A: 4-(p-hydroxyphenoxy)-N-(α-methylphenethyl)phenethylamine hydrochloride;
- Product B: 4-(p-hydroxyphenoxy)-N-(α-methylphenethyl)phenethylamine lactate.

1) Determination of acute toxicity:

The acute toxicity was determined on batches of 5 male Swiss mice having an average weight of 20 g.

The mice were kept under observation for twenty-four hours for the IV route and forty-eight hours for the IP route. The LD_{50} (50% Lethal Dose) was determined using the Karber Method.

The results obtained are as follows:

LD_{50} mg/kg	Intravenous Route	Intraperitoneal Route
Product A	36	200
Product B	46	200

2) Determination of vasodilating activity

Determination was made of the effects of products A and B on the perfusion pressure in the rear paws of dogs.

Adult dogs of both sexes weighing 11-16 kg were anesthetized with chloralose (125 mg/kg via intravenous route).

Their tracheas were intubated and the animals were mechanically ventilated. After administration of heparin, their right femoral arteries were catheterized and the blood flowing out of them, after passing through an external circuit and being reintroduced into their left femoral arteries, perfused their left rear paws, at a rate that was regulated so as to balance the carotid pressure.

Then, their left rear paws were placed in ice, which brought about an increase in the perfusion pressure. The product being studied was then injected at various doses and the variations in perfusion pressure were recorded. The average percentage decreases in the perfusion pressure were calculated for the same dose of the product injected.

The following results were obtained:

Doses in mg/kg	% Decrease in perfusion pressure in dogs' paws	
	Product A	Product B
0.03	7.6	-
0.1	15	12.3
0.3	21.7	25.2
1	24.2	35.5
3	33.3	-

These results demonstrate the clear peripheral vasodilating activity of products A and B.

Claims

1. 4-(p-hydroxyphenoxy)-N-(α-methylphenethyl)phenethylamine as well as its acid addition salts.

2. 4-(p-hydroxyphenoxy)-N-(α-methylphenethyl)phenethylamine.

3. 4-(p-hydroxyphenoxy)-N-(α-methylphenethyl)phenethylamine hydrochloride.

4. 4-(p-hydroxyphenoxy)-N-(α-methylphenethyl)phenethylamine lactate.

5. Method of preparing 4-(p-hydroxyphenoxy)-N-(α-methylphenethyl)phenethylamine and its salts, characterized in that p-hydroxyphenoxyphenethylamine is reacted with benzyl methyl ketone, in the presence of a reducing agent, in order to obtain 4-(p-hydroxyphenoxy)-N-(α-methylphenethyl)phenethylamine which, if desired, is treated with an inorganic or organic acid to form the salt thereof.

6. Method of preparation according to Claim 5, characterized in that the p-hydroxyphenoxy phenethylamine is produced *in situ* via the action of an inorganic or organic base on a salt of p-hydroxyphenoxyphenethylamine.

7. As a medication, 4-(p-hydroxyphenoxy)-N-(α-methylphenethyl)phenethylamine, as well as its pharmaceutically acceptable acid addition salts.

8. As a medication, 4-(p-hydroxyphenoxy)-N-(α-methylphenethyl)phenethylamine.

9. As a medication, 4-(p-hydroxyphenoxy)-N-(α-methylphenethyl)phenethylamine hydrochloride.

10. As a medication, 4-(p-hydroxyphenoxy)-N-(α-methylphenethyl)phenethylamine lactate.

11. The pharmaceutical compositions containing, as an active principal, at least one of the medications defined in Claims 7-10.